

# Norfloxacin Penetration into Human Renal and Prostatic Tissues

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**Concurrent norfloxacin concentrations in serum, kidney, and prostatic tissue were determined in 14 patients. Mean ratios of norfloxacin concentration in tissue over concentration in serum were  $6.6 \pm 2.8$  for the kidney and  $1.7 \pm 0.2$  for the prostate samples. The levels were above the MICs of most urinary pathogens.**

Norfloxacin, a new quinolone derivative which has good antimicrobial activity against most urinary pathogens, including gram-negative and gram-positive microorganisms (5-7) appears to be a promising agent for the treatment of urinary tract infections (5). In this study, the penetration of norfloxacin into renal and prostatic tissue was evaluated in patients undergoing nephrectomy or prostatectomy.

Fifteen patients received one 400-mg tablet of norfloxacin between 21:00 h and 22:00 h the night before surgery and a second 400-mg tablet with their premedication about 1 h before the operation. Patient 2 was removed from the study because he had received trimethoprim-sulfamethoxazole within 72 h of surgery. Table 1 summarizes the data for the 14 evaluable patients (13 males, 1 female). They were aged 53 to 83 years, with a mean of 68 years. Their mean weight was 72.5 kg (55.9 to 93.5 kg). Surgical procedures included 10 transurethral resections (TUR) in patients with benign

dose of norfloxacin. Urine samples were collected before the first tablet was given to the patient, between 0 to 12 h after the first dose, and 12 to 24 h after the second dose. Assay of norfloxacin was done by using a microbiological method with *Klebsiella pneumoniae* MB480 derived from ATCC 10031 as the test microorganism on Mueller-Hinton agar (Difco Laboratories). Urine samples were diluted 1:2 in 0.1 N hydrochloric acid to dissolve all drug crystals and then in 1% phosphate buffer (pH 6.0) as needed. Standards were prepared in pooled serum for serum and in 1% phosphate buffer (pH 6.0) for urine. Prostatic tissues were rinsed three times in saline solution, sponged, and weighed. Tissues were then finely chopped with a scalpel and incubated at 37°C for 6 h in a known volume of enzyme solution (Collagenase, 40 mg %, and hyaluronidase, 100 mg%, in 1% phosphate buffer [pH 6.0]) to facilitate homogenization, the latter being done at 4°C with a Virtis 45 homogenizer (Virtis Research Equip-

TABLE 1. Norfloxacin concentration in human tissues

Patient no.	Sex	Age (yr)	Wt (kg)	Diagnosis	Surgical procedure	Tissue sampled	Sampling time after dose 2	Concn in:			
								Tissue ( $\mu\text{g g}^{-1}$ )	Serum ( $\mu\text{g ml}^{-1}$ )	Tissue/serum ratio	Urine ( $\mu\text{g ml}^{-1}$ )
12	M	78	65.5	Vesical cancer + urethral obstruction	Right nephrectomy	Kidney	1:52	16.2	4.30	3.8	151.5
1	F	74	81.0	Coral calculus of right kidney	Right nephrectomy	Kidney	3:00	15.1	4.00	3.8	202.0
4	M	61	72.6	Grawitz tumor of left kidney	Left nephrectomy	Kidney	6:30	3.9	0.32	12.2	NS <sup>a</sup>
10	M	61	77.0	BPH	TUR	Prostate	1:00	<0.25	<0.25		87.0
8	M	63	93.5	BPH	TUR	Prostate	1:00	2.10	0.95	2.2	NS
6	M	56	67.8	BPH	TUR	Prostate	1:10	0.75	0.42	1.8	NS
5	M	60	81.5	BPH	TUR	Prostate	1:20	1.00	0.48	2.1	NS
9	M	71	55.9	BPH	TUR	Prostate	1:20	4.65	5.30	0.9	122.2
7	M	78	64.5	BPH	TUR	Prostate	1:23	0.75	0.58	1.3	NS
13	M	83	77.3	BPH	TUR	Prostate	1:25	2.00	2.20	0.9	141.8
14	M	76	67.7	BPH	TUR	Prostate	1:50	2.25	2.00	1.1	344.0
15	M	53	84.0	BPH	TUR	Prostate	1:53	1.14	0.70	1.6	79.5
11	M	59	68.0	BPH	TUR	Prostate	1:57	1.05	0.42	2.5	92.1
3	M	76	58.5	BPH + obstruction	Suprapubic resection	Prostate	5:38	2.55	1.05	2.4	NS

<sup>a</sup> NS, No specimen

prostatic hypertrophy (BPH) and a suprapubic prostatectomy in one patient with obstruction. The three remaining patients had nephrectomies. Serum was taken at the time of anesthesia administration, at the same time as tissue sampling, at the end of surgery, and 12 h after the second

ment New York). To ensure that the above procedure did not influence our results, various concentrations of norfloxacin were incubated for 24 h at 37°C in the enzymatic solution. The norfloxacin recovery after incubation was  $96.3 \pm 5.1\%$ . Standard curves were prepared by using a pool of prostatic tissue containing no antibiotics prepared as described previously (2). Kidney samples were separated into

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TABLE 2. Norfloxacin concentration in human kidney and serum

Patient no.	Concn in serum ( $\mu\text{g g}^{-1}$ )	Concn ( $\mu\text{g g}^{-1}$ ) in kidney:		
		Cortex	Medulla	Papilla
12	4.30	16.8	17.7	6.5
1	4.0	18.0	21.6	ND <sup>a</sup>
4	0.32	4.8	4.1	ND

<sup>a</sup> ND, Not done.

cortex, medulla, and papilla; rinsed with saline solution; sponged; weighed; and homogenized at 4°C (Virtis) in a known volume of 1% phosphate buffer (pH 6.0). Standard curves for kidney tissue were prepared in 1% phosphate buffer (pH 6.0). All samples (urine, tissue, and serum) were assayed in triplicate and incubated at 28°C overnight before inhibition zones were measured (2a).

A total of 51 serum samples (13 taken at the time of anesthesia administration, 14 taken at the time of tissue extraction, 13 taken at the end of surgery, and 11 taken at 12 h after the second dose), 18 urine samples (8 taken before therapy, 8 taken at 0 to 12 h after the first dose, and 2 taken at 12 to 24 h after the second dose), and 14 tissue samples (3 kidneys and 11 prostates) were analyzed.

Norfloxacin concentration in serum at the time of tissue extraction varied from  $<0.25$  to  $5.3 \mu\text{g ml}^{-1}$  (Table 1). At 12 h after the second dose of norfloxacin, the mean serum level was  $0.77 \pm 0.26 \mu\text{g ml}^{-1}$ . A mean urinary level of  $152 \mu\text{g}$  of norfloxacin  $\text{ml}^{-1}$  was detected in the urine samples collected from 0 to 12 h after the first dose. In the two patients from which urine was collected 12 to 24 h after therapy, the concentrations were 188.2 and  $532.5 \mu\text{g ml}^{-1}$ , respectively. With the exception of one sample (patient 2), no antibiotics were detected in any of the urine taken before the administration of norfloxacin. Although norfloxacin was undetectable in the serum of patient 10, the concentration in his urine was  $87 \mu\text{g ml}^{-1}$ . The levels of norfloxacin in the kidney parenchyma were strikingly higher than in prostatic tissue and reached values up to 12 times the levels in serum. The drug was distributed throughout all three regions of the kidney, i.e., cortex, medulla, and papilla (Table 2).

Norfloxacin was detectable in 9 of the 10 prostate specimens obtained by TUR. The mean concentration in the 10 patients was  $1.6 \pm 0.4 \mu\text{g g}^{-1}$ . In the tissue removed by suprapubic prostatectomy, the concentration of norfloxacin was  $2.55 \mu\text{g g}^{-1}$ . The lower value observed during TUR can be explained by the dilution of the antibiotic owing to repeated tissue flushing during the course of transurethral procedure. All patients tolerated the drug very well, and no side effect was noted.

The present study demonstrates that norfloxacin, which is now used in clinical trials in upper and lower urinary tract infections (4, 8, 9), penetrates renal and prostatic tissue. Indeed, the mean ratio of norfloxacin tissue concentration over serum concentration was  $6.6 \pm 2.8$  for the kidneys and  $1.7 \pm 0.2$  for the prostates. Prostatic concentrations of  $2.1 \mu\text{g g}^{-1}$  were also observed by Lambert and Jaupitre (T. E. Lambert and A. Jaupitre, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 24th, Washington, D.C., abstr. no. 771, 1984). Urinary concentrations and the amount of drug recovered over 12 h were identical to those reported

by others (10). With the use of high-pressure liquid chromatography method, Rogers has identified five metabolites in the urine of patients receiving norfloxacin (W. D. Rogers, Proc. 13th Int. Congr. Chemother. SS 4.6/9, part 38, p. 19-23, 1983). Although 30% of the total dose of norfloxacin administered is excreted unchanged in the urine, approximately 8 to 10% is metabolized drugs. Of these metabolites,  $M_3$  has about 1/5 of the microbiological activity of norfloxacin, and there might have been some minor interference with the biological assay. We cannot exclude the possibility that we could have under- or overestimated the concentrations within the urine or even the kidneys.

Thus, this investigation suggests that this antibiotic readily diffuses from serum into prostatic tissue. Its low protein binding (5%), its high lipid solubility (1), and its zwitterion nature with  $\text{pK}_a$ 's of 6.4 and 8.7 may favor entrapment in the human prostatic environment, in which the pH is  $7.28 \pm 0.04$  for the normal individual (3). Of most importance in this study was the observation that norfloxacin concentrations in serum, cortex, medulla, papilla, and prostate were significantly greater than the MICs for most urinary pathogens (5), suggesting that this new quinolone may be effective in the treatment of severe prostatitis and pyelonephritis.

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